blood advances

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
bloodadvances@hematology.org

# CD19-directed CART Therapy for T cell/Histiocyte Rich Large B-cell Lymphoma

Tracking no: ADV-2024-013863R1

Priyanka Pophali (University of Wisconsin Carbone Cancer Center, United States) Joshua Fein (Weill Cornell Medicine/NewYork Presbyterian Hospital, United States) Kwang Ahn (Medical College of Wisconsin, United States) Molly Allbee-Johnson (Medical College of Wisconsin, United States) Nausheen Ahmed (University of Kansas Cancer Center, United States) Farrukh Awan (UT Southwestern, United States) Shatha Farhan (Henry Ford Healthsystem, United States) Natalie Grover (Lineberger Comprehensive Cancer Center, University of North Carolina, United States) Talal Hilal (Mayo Clinic, United States) Madiha Iqbal (Mayo Clinic Florida, United States) Joeseph Maakaron (University of Minnesota, United States) Dipenkumar Modi (Barbara Ann Karmanos Cancer Institute, Wayne State University, United States) Elham Nasrollahi (University of Pittsburgh Medical Center in Central PA, United States) Levanto Schachter (Oregon Health and Science University, United States) Craig Sauter (Cleveland Clinic, United States) Mehdi Hamadani (Medical College of Wisconsin, United States) Alex Herrera (City of Hope, United States) Roni Shouval (Memorial Sloan Kettering Cancer Center, United States) Mazyar Shadman (Fred Hutchinson Cancer Research Center, United States)

**Abstract:**
T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) is a rare histologic variant of LBCL. Limited data regarding CD19-directed chimeric antigen receptor T-cell (CART) therapy in relapsed/refractory (R/R) THRLBCL suggest poor efficacy. We investigated CART outcomes for R/R THRLBCL through the CIBMTR registry. A total of 58 adult patients with R/R THRLBCL who received commercial CD19-CART between 2018-2022 were identified. Most patients (67%) had early relapse of disease (45% primary refractory) with a median of 3 (range: 1-7) prior therapies and were treated with Axicabtagene ciloleucel (69%). At median follow-up of 23 months post-CART, 2-year overall and progression-free survival were 42% (95% CI: 27-57) and 29% (95% CI: 17-43), respectively. In univariable analysis, poor performance status pre-CART was associated with higher mortality (HR 2.35, 95%CI 1.02-5.5). The 2-year cumulative incidences of relapse/progression and non-relapse mortality were 69% and 2%, respectively. Grade {greater than or equal to}3 CRS and ICANS occurred in 7% and 15% of patients, respectively. In this largest analysis of CD19-CART for R/R THRLBCL, approximately 30% of patients were alive and progression-free 2 years post-CART. Despite a high incidence of progression (69% at 2 years), these results suggest a subset of patients with R/R THRLBCL may have durable responses with CART.

**Conflict of interest:** COI declared - see note

**COI notes:** Mehdi Hamadani reports research support/Funding: Takeda Pharmaceutical Company; ADC Therapeutics; Spectrum Pharmaceuticals; Astellas Pharma. Consultancy: ADC Therapeutics, Omeros, CRISPR, BMS, Kite, AbbVie, Caribou, Genmab. Speaker's Bureau: ADC Therapeutics, AstraZeneca, Bei Gene, Kite. DMC: Inc, Genentech, Myeloid Therapeutics, CRISPR Craig Sauter has served as a paid consultant: Kite/a Gilead Company, Celgene/BMS, Gamida Cell, Karyopharm Therapeutics, Ono Pharmaceuticals, MorphoSys, CSL Behring, Syncopation Life Sciences, CRISPR Therapeutics, Ipsen Biopharmaceuticals, Inc. and GSK. He has received research funds for clinical trials from: Juno Therapeutics, Celgene/BMS, Bristol-Myers Squibb, Precision Biosciences, Actinium Pharmaceuticals, Sanofi-Genzyme and NKARTA. Mazyar Shadman reports Consulting, Advisory Boards, steering committees or data safety monitoring committees: AbbVie, Genentech, AstraZeneca, Janssen, Beigene, Bristol Myers Squibb, Morphosys/Incyte, Kite Pharma,Eli Lilly, Mustang Bio, Fate therapeutics, Nurix, Merck. Research Funding: Mustang Bio, Genentech, AbbVie, Beigene, AstraZeneca, Genmab, Morphosys/Incyte, Vincerx .Stock options: Koi Biotherapeutics. Employment: Bristol Myers Squibb (spouse) Joseph Maakaron reports grants or contracts from Gilead, Atara, CRISPR, Precision Biosciences, and Scripps Research Institute. Talal Hilal reports consulting fees from BeiGene. Priyanka Pophali reports consulting fees from SeaGen.

**Preprint server:** No;

**Author contributions and disclosures:** P.P., J.A.F., R.S., M.S., A.H., and M.H. conceived and designed the paper. M.A.J. and M.H. collected and assembled the data. Data analysis was performed by M.H., M.A.J., and K.W.A. P.P. wrote the initial draft of the manuscript, and all authors contributed to revising the manuscript.

**Non-author contributions and disclosures:** No;

**Agreement to Share Publication-Related Data and Data Sharing Statement:** The Center for International Blood and Marrow Transplant Research (CIBMTR) supports accessibility of research in accord with the National Institutes of Health Data Sharing Policy and the National Cancer Institute Cancer Moonshot Public Access and Data Sharing Policy. The CIBMTR only releases deidentified data sets that comply with all relevant global regulations regarding privacy and confidentiality.

**Clinical trial registration information (if any):**

**Title:** CD19-directed CART Therapy for T cell/Histiocyte Rich Large B-cell Lymphoma

**Running title:** CART for THRLBCL

**Authors:** Priyanka A. Pophali[1*], Joshua A. Fein[2*], Kwang W. Ahn[3], Molly Allbee-Johnson[4], Nausheen Ahmed[5], Farrukh T. Awan[6], Shatha Farhan[7], Natalie S. Grover[8], Talal Hilal[9], Madiha Iqbal[10], Joseph Maakaron[11], Dipenkumar Modi[12], Elham Nasrollahi[13], Levanto G. Schachter[14], Craig Sauter[15], Mehdi Hamadani [4,16], Alex Herrera[17], Roni Shouval[18,19], Mazyar Shadman[20]

*Authors contributed equally and share first authorship.

**Affiliations:**

1. Division of Hematology, Medical Oncology & Palliative Care, University of Wisconsin, Carbone Cancer Center, Madison, WI
2. Division of hematology and Oncology, Weill Cornell Medicine, New York, NY
3. Division of Biostatistics, Institute for Health and Equity, Medical College of Wisconsin, Milwaukee, WI
4. Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI
5. Division of Hematologic Malignancies and Cellular Therapeutics, The University of Kansas Cancer Center
6. Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center
7. Henry Ford Health System Stem Cell Transplant & Cellular Therapy Program
8. University of North Carolina
9. Mayo Clinic Arizona
10. Mayo Clinic Florida
11. University of Minnesota
12. Karmanos Cancer Institute, Wayne State University
13. Department of Internal Medicine, University of Pittsburgh Medical Center in Central Pa., Harrisburg, PA
14. University of California Los Angeles
15. Blood and Marrow Transplant program, Department of Hematology and Medical Oncology, Taussig Cancer Center, Cleveland Clinic, Cleveland, Ohio, USA.
16. BMT & Cellular Therapy Program, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI
17. Division of Lymphoma, Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, Duarte, CA
18. Department of Medicine, Adult Bone Marrow Transplantation Service, Memorial Sloan Kettering Cancer Center, New York, NY
19. Medicine, Weill Cornell Medical College, New York, NY
20. Fred Hutch Cancer Center and University of Washington, Seattle, WA

**Corresponding Author**: Mehdi Hamadani, MD, Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, 9200 W. Wisconsin Avenue, Suite C5500, Milwaukee, WI 53226, USA; Phone: 414-805-0643; Fax: 414-805-0714; E-mail: mhamadani@mcw.edu

**Data sharing statement:** The Center for International Blood and Marrow Transplant Research (CIBMTR) supports accessibility of research in accord with the National Institutes of Health Data Sharing Policy and the National Cancer Institute Cancer Moonshot Public Access and Data Sharing Policy. The CIBMTR only releases deidentified data sets that comply with all relevant global regulations regarding privacy and confidentiality.

**Abstract word count: 196**
**Article word count: 1585**
**Tables: 1**
**Figures: 2**

**Supplemental Tables: 3**

**Key Point 1:** Among 58 patients who received CD19-directed CART cells for T cell/Histiocyte Rich Large B-cell Lymphoma, the 2-year PFS was 29%.

**Abstract:**

T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) is a rare histologic variant of LBCL. Limited data regarding CD19-directed chimeric antigen receptor T-cell (CART) therapy in relapsed/refractory (R/R) THRLBCL suggest poor efficacy. We investigated CART outcomes for R/R THRLBCL through the CIBMTR registry. A total of 58 adult patients with R/R THRLBCL who received commercial CD19-CART between 2018-2022 were identified. Most patients (67%) had early relapse of disease (45% primary refractory) with a median of 3 (range: 1-7) prior therapies and were treated with *Axicabtagene ciloleucel* (69%). At median follow-up of 23 months post-CART, 2-year overall and progression-free survival were 42% (95% CI: 27-57) and 29% (95% CI: 17-43), respectively. In univariable analysis, poor performance status pre-CART was associated with higher mortality (HR 2.35, 95%CI 1.02-5.5). The 2-year cumulative incidences of relapse/progression and non-relapse mortality were 69% and 2%, respectively. Grade ≥3 CRS and ICANS occurred in 7% and 15% of patients, respectively. In this largest analysis of CD19-CART for R/R THRLBCL, approximately 30% of patients were alive and progression-free 2 years post-CART. Despite a high incidence of progression (69% at 2 years), these results suggest a subset of patients with R/R THRLBCL may have durable responses with CART.

## INTRODUCTION:

T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) is a rare histologic variant that comprises <10% of LBCL and is classified as a separate entity based on the morphologically distinct appearance (1). The 5$^{th}$ edition of WHO classification considers THRLBCL at the extreme end of a spectrum of growth patterns of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) with a more aggressive clinical behavior (2). NLPHL and THRLBCL also share highly recurrent genetic lesions supporting a close relationship(3, 4) and distinguishing between these entities can be challenging. Due to limited available evidence regarding subtype-specific outcomes in patients with THRLBCL, they are managed like diffuse LBCL (DLBCL) in the frontline and relapsed settings.

A study of the tumor microenvironment (TME) in THRLBCL biopsy samples identified PD-1/PD-L1 signaling as a possible pathogenic mechanism and driver of immune escape (5). Although retrospective studies in the rituximab era have reported survival rates comparable to DLBCL with intensive chemo-immunotherapy (6, 7), the treatment of relapsed disease remains an unmet need due to poor outcomes (8). While CD19-directed chimeric antigen receptor T-cell (CART) therapy has shown efficacy in relapsed/refractory (R/R) DLBCL (9-12), its role in THRLBCL remains largely undefined. In published case series of patients with R/R THRLBCL, almost all patients experienced early treatment failure post-CART infusion (8, 13). These reports have brought into question the role of anti-CD19 CART therapy in R/R THRLBCL, especially as we have learned more about its unique TME. Therefore, we investigated the outcomes of patients with R/R THRLBCL treated with FDA-approved commercial CART in the real world through the Center for International Blood and Marrow Transplant Research (CIBMTR) registry.

## METHODS

### Data source

The CIBMTR is a working group comprised of over 380 transplantation centers worldwide that provide data regarding cellular therapies to a statistical center at the Medical College of Wisconsin (MCW). Data quality is augmented through computerized affirmation of discrepancies, physicians' review of submitted data, and on-site audits of participating centers. Observational studies are conducted by the CIBMTR in compliance with all pertinent federal regulations with regard to protection of human research participants. All patients included in this analysis have provided written consent for research. The Institutional Review Board of MCW has approved this study. Patient provide informed consent for their data to be reported to CIBMTR.

**Patients**

Adult patients (≥18 years) with THRLBCL who received FDA-approved commercial CD19-directed CART products (*axicabtagene ciloleucel or axi-cel, tisagenlecleucel or tisa-cel, lisocabtagene maraleucel or liso-cel*) as their first cell therapy infusion between 2018 and 2022 were identified in the CIBMTR registry. Patients were excluded if they had received prior adoptive cellular therapy, not consented for research, or treated at embargoed or European Union centers.

**Definitions and endpoints**

Overall survival (OS) was the primary outcome. Patients alive without evidence of disease relapse or progression were censored at last follow-up. Death from any cause was considered an event for OS analysis. Secondary outcomes included progression-free survival (PFS), cumulative incidence of progression/relapse (CIP/R), non-relapse mortality (NRM), incidence of cytokine release syndrome (CRS) and immune-effector-cell-associated neurologic syndrome (ICANS). For PFS, progression/relapse or death from any cause were considered events. NRM was defined as death without evidence of prior lymphoma progression/relapse; relapse was

considered a competing risk. CIP/R was defined as relapsed lymphoma after CART; NRM was considered a competing risk. Bridging was defined as any therapy, including radiation, administered between apheresis and CART infusion, or patients' last line of treatment before CART if it was continued after apheresis. Disease response to last line of therapy at the time before CART was defined using the Lugano Classification(14, 15).

**Statistical analysis**

Baseline characteristics of the study population were described. CRS and ICANS were reported according to the consensus ASTCT criteria (16). Kaplan-Meier estimates were used for OS and PFS. Forest plots were created to present hazard ratios and their 95% confidence intervals based on the univariable Cox model. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

## RESULTS

A total of 58 patients from 37 centers met the study inclusion criteria and were included in the analysis. Baseline patient and disease characteristics are summarized in Table 1. Prior to CART, 17 (29%) patients had bulky disease (>5 cm), and 12 (21%) had bone marrow involvement. The median age at CART infusion was 49 years (range: 19-76), with 12 patients (21%)>65 years. Patients were predominately male (79%), white (69%) and non-Hispanic/non-Latino (88%). One-third of patients (N=19) had a comorbidity score(17) of ≥3 and 24 (41%) had a Karnofsky performance status (KPS) <90. Most patients (N=39, 67%) had early relapse of TCHRBCL (within 12 months of first-line therapy), including 26 (45%) with primary refractory disease. The median number of prior therapies was 3 (range: 1-7), which included 21 (36%) patients with prior autologous stem cell transplantation (SCT) and 1 (2%) patient with prior allogeneic SCT.

*Axi-cel* was the predominant CART product (N=40, 69%), followed by *Tisa-cel* (N=15, 26%) and *liso-cel* (N=3, 5%). Bridging therapy was reported in 18 (31%) patients, most commonly multi- or single-agent chemotherapy (23%). Almost all patients (93%) had active disease pre-CART; only 4 patients were in complete remission (CR).

CRS was reported to occur in 40 (69%) patients: 26 (45%) grade 1, 10 (17%) grade 2, 2 (3%) grade 3, and 1 (1.7%) each grade 4 and 5. ICANS was reported in 17 (29%) patients: 5 (9%) grade 1, 3 (5%) grade 2, 4 (7%) grade 3, 5 (9%) grade 4 (Supplemental Table 1). By day 100 post-CART, best overall response rate (ORR) was 50% with 28% CR and 22% partial responses (PR). ORR and CR rates were similar between CART products (Supplemental Table 2).

With a median follow-up of 23 months (range: 2-48) from CART infusion, 2-year OS was 42% (95% CI: 27-57), and PFS was 29% (95% CI: 17-43; Figure 1). Among patients who achieved a CR as of day 100, the 2-year cumulative incidence of relapse was 33% (95% CI: 5-71%), corresponding to a 2-year OS and PFS among these patients of 92% (95% CI: 73-100%) and 67% (95% CI: 32-94%), respectively. Considering only those patients who were not already in CR at infusion (n = 54), the 2-year OS and PFS were 39% (95% CI: 24-56) and 25% (95% CI: 12-40%), respectively.

In a univariable analysis, there were no significant associations with PFS or OS except KPS<90 pre-CART infusion, which was associated with significantly higher risk for mortality HR 2.37 (95% CI 1.02-5.5) (Figure 2). The 2-year CIP/R was 69% (95% CI: 55-82) and NRM was 2% (95% CI: 0-8). A total of 30 deaths were reported during the follow-up period, with lymphoma recurrence/progression, seen in 23 (77%) patients, being the most common cause of death (Supplemental Table 3).

## DISCUSSION

THRLBCL is a rare aggressive histologic subtype of LBCL. The pivotal clinical trials that led to the approval of CART products (*axi-cel, tisa-cel, liso-cel*) predominantly enrolled patients with the DLBCL, NOS histology(11, 12, 18). CD19-directed CART can be used for treating patients with R/R THRLBCL; however, its therapeutic efficacy is not well established. In this largest study to date of R/R THRLBCL treated with CART therapy, we found that nearly 30% of patients were alive and progression-free 2-years post-CART. The day-100 post-CART ORR and CR rates were 50% and 28%, respectively. Prior real-world analysis from the CIBMTR of patients treated with *axi-cel*(19) and *tisa-cel*(20) for R/R LBCL have reported higher day-100 ORR 60-73% and CR rates 44-56% but similar 2-year PFS 28-36% and OS 44-45%. Thus, post-CART outcomes of patients with R/R THRLBCL overall appear potentially less favorable than DLBCL but some patients do experience durable responses.

As our understanding of the TME of THRLBCL increases, future therapeutic options may emerge. Griffin et al. found that malignant THRLBCL B-cells can have PDL1/PDL2 copy gain or amplification in 64% of cases associated with increased PD-L1 expression. Their study also reported clinical responses to PD-1 blockade in 3 of 5 patients with R/R THRLBCL, including 2 CR and 1 PR (5). A multi-center case series by Trujillo et al. reported that 9 out of 9 patients with THRLBCL had progressive disease by day-90 post-CART (13). They noted evidence of adequate CART expansion in 3/3 cases studied and CD19 expression remained intact on 5/5 assessable cases on progression post-CART. The authors observed high co-expression of PD-1 and observed objective responses in 2 out of 5 patients treated with anti-PD-1 therapy post-CART progression. Thus, they hypothesized that THRLBCL is inherently CART-resistant due to its unique TME. Checkpoint inhibitor therapy with anti-PD-1 antibodies is uncommonly utilized for patients with relapsed aggressive LBCL due to low efficacy, including in the post-CART setting (21, 22). However, it is possible that in certain histologies such as THRLBCL in which there is a biological rationale, combining PD1 blockade with CD19-CART may be a reasonable

approach to try and overcome CAR-T resistance. Trials are currently underway to investigate this strategy (NCT05934448).

Our study has limitations inherent to real-world studies, such as lack of central confirmation of pathologic diagnosis (including history of NLPHL), missing details on disease burden (e.g. LDH) as well as bridging and subsequent therapies post-CART progression, day-30 post-CART response, duration of response and loss to follow-up. However, this is the largest cohort of R/R THRLBCL treated with CART therapy with 93% and 86% patients having 1- and 2-year post-CART follow-up, respectively.

In summary, our study found that ~30% of patients with R/R THRLBCL may have durable responses with CART indicating that CD19-directed CART remains a potentially curative therapeutic option for this rare disease. However, the risk of progression remains high. Current research is evaluating combination strategies with anti-PD1 antibodies to improve outcomes for patients with THRLBCL.

**ACKNOWLEDGEMENTS:**

The CIBMTR is supported primarily by Public Health Service U24CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID); HHSH250201700006C from the Health Resources and Services Administration (HRSA); and N00014-20-1-2705 and N00014-20-1-2832 from the Office of Naval Research; Support is also provided by Be the Match Foundation, the Medical College of Wisconsin, the National Marrow Donor Program, and from the following commercial entities: Actinium Pharmaceuticals, Inc.; Adienne SA; Allovir, Inc.; Amgen, Inc.; Angiocrine Bioscience; Astellas Pharma US; bluebird bio, Inc.; Bristol Myers Squibb Co.; Celgene Corp.; CSL Behring; CytoSen Therapeutics, Inc.; Daiichi Sankyo Co., Ltd.; ExcellThera; Fate Therapeutics; Gamida-Cell, Ltd.; Genentech Inc; Incyte Corporation; Janssen/Johnson & Johnson; Jazz Pharmaceuticals, Inc.; Kiadis Pharma; Kite, a Gilead Company; Kyowa Kirin; Legend Biotech; Magenta Therapeutics; Merck Sharp & Dohme Corp.; Millennium, the Takeda Oncology Co.; Miltenyi Biotec, Inc.; Novartis Pharmaceuticals Corporation; Omeros Corporation; Oncoimmune, Inc.; Orca Biosystems, Inc.; Pfizer, Inc.; Pharmacyclics, LLC; Sanofi Genzyme; Stemcyte; Takeda Pharma; Vor Biopharma; Xenikos BV. RS is supported in part through the National Institutes of Health (NIH)/National Cancer Institute (NCI) Cancer Center Support Grant P30 CA008748 and an NIH-NCI K-award (K08CA282987).

**AUTHOR CONTRIBUTIONS:**

**Conception and design**: Priyanka Pophali, Joshua Fein, Roni Shouval, Mazyar Shadman, Alex Herrera and Mehdi Hamadani

**Financial support**: CIBMTR

**Collection and assembly of data**: Mariam Allbee-Johnson and Mehdi Hamadani

**Data analysis**: Mehdi Hamadani, Marian Allbee-Johnson & Kwang W. Ahn.

**Interpretation**: All authors.

**Manuscript writing**: First draft prepared by Priyanka Pophali. All authors helped revise the manuscript.

**Final approval of manuscript**: All authors

**Disclosure of conflict of interest**:

Mehdi Hamadani reports research support/Funding: Takeda Pharmaceutical Company; ADC Therapeutics; Spectrum Pharmaceuticals; Astellas Pharma. Consultancy: ADC Therapeutics, Omeros, CRISPR, BMS, Kite, AbbVie, Caribou, Genmab, Autolus. Speaker's Bureau: ADC Therapeutics, AstraZeneca, Bei Gene, Kite. DMC: Inc, Genentech, Myeloid Therapeutics, CRISPR

Craig Sauter has served as a paid consultant: Kite/a Gilead Company, Celgene/BMS, Gamida Cell, Karyopharm Therapeutics, Ono Pharmaceuticals, MorphoSys, CSL Behring, Syncopation Life Sciences, CRISPR Therapeutics, Ipsen Biopharmaceuticals, Inc. and GSK. He has received research funds for clinical trials from: Juno Therapeutics, Celgene/BMS, Bristol-Myers Squibb, Precision Biosciences, Actinium Pharmaceuticals, Sanofi-Genzyme, Cargo Therapeutics and NKARTA.

Mazyar Shadman reports Consulting, Advisory Boards, steering committees or data safety monitoring committees: AbbVie, Genentech, AstraZeneca, Janssen, Beigene, Bristol Myers Squibb, Morphosys/Incyte, Kite Pharma,Eli Lilly, Mustang Bio, Fate therapeutics, Nurix, Merck. Research Funding: Mustang Bio, Genentech, AbbVie, Beigene, AstraZeneca, Genmab, Morphosys/Incyte, Vincerx .Stock options: Koi Biotherapeutics. Employment: Bristol Myers Squibb (spouse)

Joseph Maakaron reports grants or contracts from Gilead, Atara, CRISPR, Precision Biosciences, and Scripps Research Institute.

Talal Hilal reports consulting fees from BeiGene.

Priyanka Pophali reports consulting fees from SeaGen.

Natalie Grover reports consulting fees from Kite, BMS, Seagen, ADC Therapeutics, Caribou Biosciences and participation on data safety monitoring board or advisory board for Novartis.

Levanto Schachter reports serving on a data safety monitoring board for an IIT at OHSU Myeloma group without associated payments.

Farrukh Awan reports consulting fees from Genentech, Astrazeneca, Abbvie, Janssen, Pharmacyclics, Gilead sciences, Kite pharma, Celgene, Karyopharm, MEI Pharma, Verastem, Incyte, Beigene, Johnson and Johnson, Dava Oncology, BMS, Merck, Cardinal Health, ADCT therapeutics, Loxo Oncology, Adaptive Biotechnologies, Genmab, Epizyme, Caribou Biosciences, Cellecter Bisosciences. He has participated on a data safety monitoring board or advisory board for Ascentage and Astra Zaneca.

Dipenkumar Modi reports consulting fees from AstraZaneca (self and spouse), honoraria from Beigene, participation in data safety monitoring board or advisory board for Genmab, ADC therapeutics, Seagen and Genentech (spouse).

Nausheen Ahmed reports consulting fees and travel support from Kite/Gilead and honoraria from Nebraska Medical Oncology.

**The other authors reported no conflicts of interest to disclose**.

## References


1. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-90.

2. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-48.

3. Hartmann S, Doring C, Jakobus C, Rengstl B, Newrzela S, Tousseyn T, et al. Nodular lymphocyte predominant hodgkin lymphoma and T cell/histiocyte rich large B cell lymphoma--endpoints of a spectrum of one disease? PLoS One. 2013;8(11):e78812.

4. Schuhmacher B, Bein J, Rausch T, Benes V, Tousseyn T, Vornanen M, et al. JUNB, DUSP2, SGK1, SOCS1 and CREBBP are frequently mutated in T-cell/histiocyte-rich large B-cell lymphoma. Haematologica. 2019;104(2):330-7.

5. Griffin GK, Weirather JL, Roemer MGM, Lipschitz M, Kelley A, Chen PH, et al. Spatial signatures identify immune escape via PD-1 as a defining feature of T-cell/histiocyte-rich large B-cell lymphoma. Blood. 2021;137(10):1353-64.

6. Robin ET DE, Batlevi CL et al. Favorable Outcomes Among Patients with T-Cell/Histiocyte-Rich Large B-Cell Lymphoma Treated with Higher-Intensity Therapy in the Rituximab Era. Blood. 2020;136:36-8.

7. Ollila TA, Reagan JL, Olszewski AJ. Clinical features and survival of patients with T-cell/histiocyte-rich large B-cell lymphoma: analysis of the National Cancer Data Base. Leuk Lymphoma. 2019;60(14):3426-33.

8. Nair R, Ogundipe I, Gunther J, Medeiros LJ, Jain P, Nastoupil LJ, et al. Outcomes in Patients with Relapsed Refractory T-Cell/Histiocyte-Rich Large B-Cell Lymphoma Treated with CAR-T Cell Therapies or Salvage Chemotherapy - a Single-Institution Experience. Blood. 2023;142(Supplement 1):6327-.

9. Kanate AS, Majhail N, DeFilipp Z, Dhakal B, Dholaria B, Hamilton B, et al. Updated Indications for Immune Effector Cell Therapy: 2023 Guidelines from the American Society for Transplantation and Cellular Therapy. Transplant Cell Ther. 2023;29(10):594-7.
10. Epperla N, Kumar A, Abutalib SA, Awan FT, Chen YB, Gopal AK, et al. ASTCT Clinical Practice Recommendations for Transplantation and Cellular Therapies in Diffuse Large B Cell Lymphoma. Transplant Cell Ther. 2023;29(9):548-55.
11. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. 2017;377(26):2531-44.
12. Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839-52.
13. Trujillo JA, Godfrey J, Hu Y, Huang J, Smith SM, Frigault MJ, et al. Primary resistance to CD19-directed chimeric antigen receptor T-cell therapy in T-cell/histiocyte-rich large B-cell lymphoma. Blood. 2021;137(24):3454-9.
14. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-68.
15. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-86.
16. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-38.

17. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005;106(8):2912-9.

18. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2019;380(1):45-56.

19. Jacobson CA, Locke FL, Ma L, Asubonteng J, Hu ZH, Siddiqi T, et al. Real-World Evidence of Axicabtagene Ciloleucel for the Treatment of Large B Cell Lymphoma in the United States. Transplant Cell Ther. 2022;28(9):581 e1- e8.

20. Daniel J. Landsburg MF, Michael Heim, Stephen Ronan Foley, Brian T. Hill, Christine M. Ho, Caron A. Jacobson, Samantha Jaglowski, Frederick L. Locke, Ron Ram, Peter A. Riedell, Gunjan L. Shah, Leslie L. Popplewell, Ranjan Tiwari, Stephen Lim, Marta Majdan, Aisha Masood, Marcelo C Pasquini, Cameron J. Turtle. Real-World Outcomes for Patients with Relapsed or Refractory (R/R) Aggressive B-Cell Non-Hodgkin's Lymphoma (aBNHL) Treated with Commercial Tisagenlecleucel: Subgroup Analyses from the Center for International Blood and Marrow Transplant Research (CIBMTR) Registry. Blood. 2022;140(Supplement 1):1584–7.

21. Major A, Yu J, Shukla N, Che Y, Karrison TG, Treitman R, et al. Efficacy of checkpoint inhibition after CAR-T failure in aggressive B-cell lymphomas: outcomes from 15 US institutions. Blood Adv. 2023;7(16):4528-38.

22. Ansell SM, Minnema MC, Johnson P, Timmerman JM, Armand P, Shipp MA, et al. Nivolumab for Relapsed/Refractory Diffuse Large B-Cell Lymphoma in Patients Ineligible for or Having Failed Autologous Transplantation: A Single-Arm, Phase II Study. J Clin Oncol. 2019;37(6):481-9.

**Table 1: Baseline characteristics of patients who underwent CART for THRLBCL reported to the CIBMTR June 2015-March 2022 (N=58)**

| Characteristic | N (%) |
|---|---|
| Age at CART infusion, years, median (range) | 49 (19-76) |
| Female sex | 12 (21) |
| Race | |
| White | 40 (69) |
| Black/African American | 11 (19) |
| Other/not reported | 7 (13) |
| Ethnicity | |
| Non-Hispanic/Non-Latino | 51 (88) |
| Hispanic/Latino | 3 (5) |
| Other/not reported | 4 (7) |
| Pre-infusion Karnofsky performance status | |
| 90-100 | 28 (48) |
| 70-80 | 22 (38) |
| < 60 | 2 (3) |
| Not reported | 6 (10) |
| HCT-CI* | |
| 0 | 17 (29) |
| 1-2 | 19 (32) |
| 3+ | 19 (33) |
| Not reported | 3 (5) |
| Bulky disease prior to CART | |
| 0 – 5 cm | 19 (33) |
| 5 – 10 cm | 13 (22) |
| > 10 cm | 4 (7) |
| Not reported | 22 (38) |
| Bone marrow involvement at diagnosis | 12 (21) |
| Received bridging therapy | |
| No | 32 (55) |
| Yes | 18 (31) |
| Not reported | 8 (14) |
| Lines of prior therapy, median (range) | 3 (1-7) |
| Prior autologous transplant | 21 (36) |
| Prior allogeneic transplant | 1 (2) |
| Product | |
| *Axicabtagene ciloleucel* | 40 (69) |
| *Tisagenlecleucel* | 15 (26) |
| *Lisocabtagene maraleucel* | 3 (5) |

*HCT-CI: hematopoietic cell transplantation-comorbidity index

**Figure legends:**

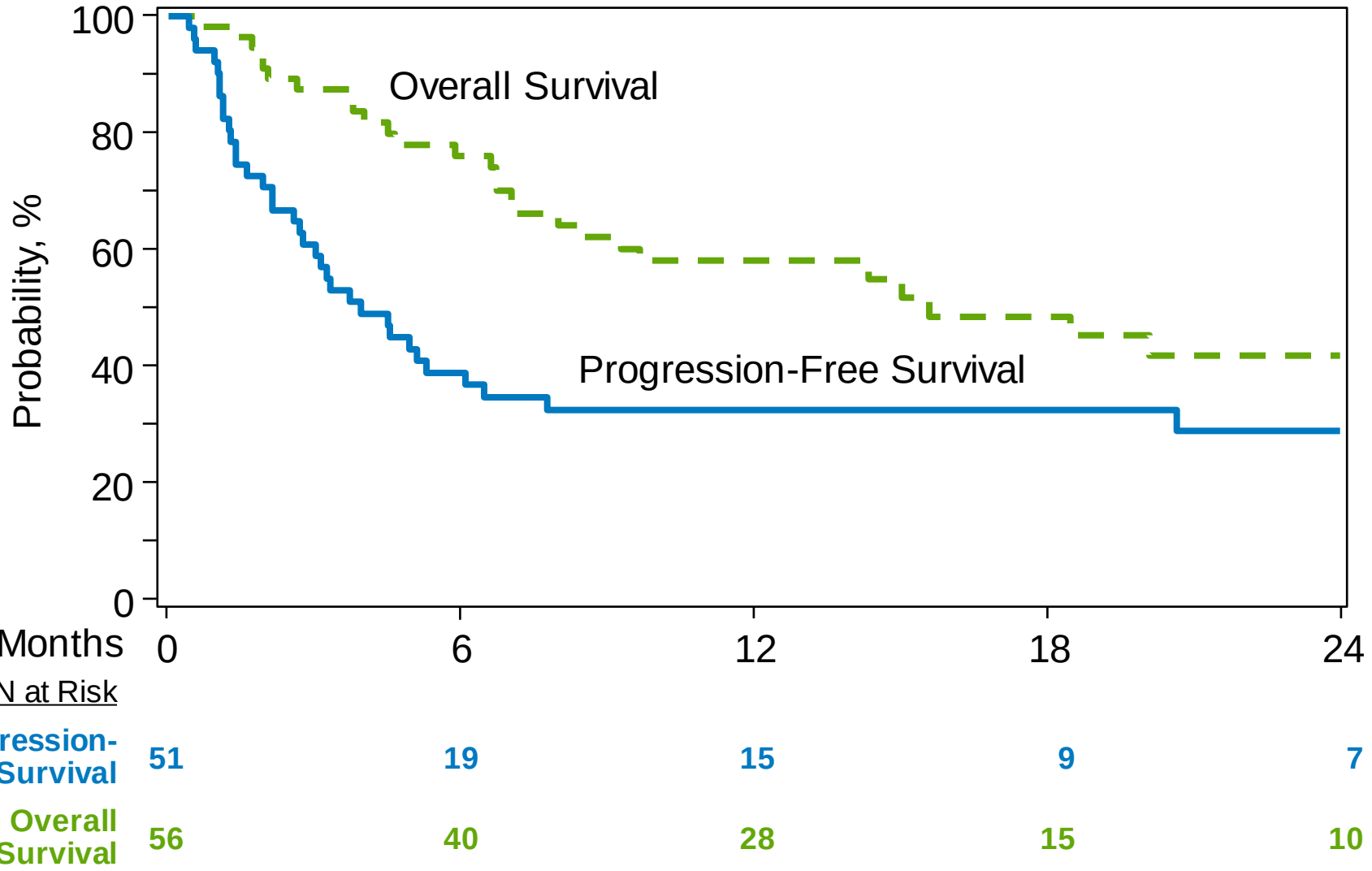
**1 - Overall and progression free survival of patients with relapsed THRLBCL treated with CD19-CART in the CIBMTR registry.**

2 - **Univariable analysis of association with (A) OS and (B) PFS**

OS: overall survival; PFS: progression:free survival; KPS: Karnofsky performance status; Tisa-cel: tisagenlecleucel; Axi-cel: axicabtagene ciloleucel; HCT - Hematopoietic cell transplantation; Allo-HCT allogeneic hematopoietic cell transplantation. Auto-HCT autologous hematopoietic cell transplantation**.**

Figure 1

# Survival




N at Risk

| | | | | | |
|---|---|---|---|---|---|
| Progression-Free Survival | 51 | 19 | 15 | 9 | 7 |
| Overall Survival | 56 | 40 | 28 | 15 | 10 |

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Figure 2